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4053-Pos Board B781
A Molecular Dynamics Simulation Study on the Effect of Endogenous Molecules on SiRNA Polyplexes
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Small interfering RNA (siRNA) based RNA interference (RNAi) is an important therapeutic strategy in treatment of cancer and hereditary diseases. RNAi is composed of several important stages, the first being siRNA delivery into cells. Polymeric carriers are used in delivery to aggregate siRNA molecules into nano-scale polyplexes. Upon delivery of polyplexes into cytosol, siRNA has to be released to trigger RNAi. However, mechanism of siRNA release from polyplexes is not clear; how endogenous molecules may affect the stability of polyplexes in cytosol is yet to be explored. In this study, we performed a series of molecular dynamics (MD) simulations to study the behavior of siRNA polyplexes in the presence of microRNA (miRNA), the most abundant nucleic acid inside cells. Polyethylenimine (PEI), known as a 'gold-standard' among polymeric delivery vehicles, was used as the carrier. miRNAs were introduced into pre-formed siRNA-PEI polyplexes. Quantitative analysis of the MD trajectories was carried out to characterize the change in the structure, compactness and charge distribution of the polyplex upon miRNA addition. PEI affinity toward siRNA and miRNA was determined and compared through individual simulations on siRNA-PEI and miRNA-PEI complexation. Data obtained from the MD simulations was compared with gel electrophoresis assays of siRNA-PEI-miRNA mixtures as well as siRNA-PEI-heparin mixtures; the latter served as a control due to the known capability of heparin to cause siRNA release. Our results revealed the ability of miRNAs to bind to pre-formed siRNA polyplexes through electrostatic interactions with PEI nitrogens. Therefore, upon the addition of miRNA, the size of the polyplex increased and its charge became negative. In agreement with the simulations, in gel electrophoresis, at the same concentrations, heparin was able to release siRNA while polyplexes maintained their integrity in the presence of miRNA.

4054-Pos Board B782
Novel Coarse-Grained Model for Molecular Dynamics Simulations of DNA
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We have developed and efficient, sequence-specific coarse-grained model to simulate the conformational motion of large double stranded DNA in molecular dynamics simulations. The DNA backbone is modeled by beads with DNA bases represented by sets of three beads, and bead positions are used to calculate the shift, slide, rise, roll, twist and tilt conformational step parameters of DNA. With these parameters, elastic deformation energies are calculated following Olson's harmonic model (Olson et. al., Proc. Natl. Acad. Sci. USA 95, 11163 (1998)). Specifics of the model and sample simulations will be discussed.

4055-Pos Board B783
Investigating the Folding Dynamics of RNA Pseudoknot Structural Motif via Massively Parallel Molecular Dynamics
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RNA pseudoknots compose a three-dimensional structural motif that is present in the catalytic cores of some ribozymes, and are also capable of stimulating ribosomal frameshifts. Their complex topology and non-canonical hairpin-loop composition make pseudoknots an ideal structural motif with which to study the RNA folding process. Here we report our analysis of nearly 20,000 independent all-atom molecular dynamics simulations of the ribosomal frame-shifting pseudoknot of Luteovirus and the tmRNA pseudoknot from Aquifex aeolicus, which share global topology but have only ~50% sequence similarity. Using the Folding@Home distributed computing network and a novel Pathway Enumeration sampling method, a cumulative sampling time of over 115 μs was achieved for each of these pseudoknots. K-means clustering identified 27 conformational microstates for each pseudoknot, which reached conformational equilibrium after ~6 ns of ensemble sampling. Multiple folding metrics were used to identify 9 macrostates participating in the folding process, including previously undescribed misfolded and intermediate states. In agreement with our previous studies of tetraloop hairpins and tRNA, the similar folding behavior of these pseudoknots suggests that native state topology is a predominant factor in the RNA folding mechanism.

4056-Pos Board B784
Hierarchical Folding of the rRNA in the Early Assembly of the E. Coli Ribosomal Small Subunit
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In order to investigate the co-transcriptional folding and assembly of the E. coli ribosomal small subunit (SSU), we applied the structure-based Go model to fold 16S rRNA fragments with increasing length. The first fragment examined is the binding domain of S20, which includes the first few local and non-local helices to be transcribed (h6, h7-h10) in vivo. The simulations show that the main barriers to the formation of the S20 binding domain are the docking of the 3' and 5' strands of the non-local h7 followed by re-orientation of the helices in the four-way junction to allow tertiary contacts between h6 and h8 to be established. These observations suggest the role of the primary binding protein S20 in stabilizing key tertiary contacts and speeding up the protein:RNA recognition during the assembly process.
Transcription of rRNA then proceeds to the local five-way junction (5WJ), which nucleates the assembly of the 5' domain upon interaction with the initiator and primary binding protein S4. This complex contains the largest contiguous ribosomal structure signature, helix h16, which is a conserved feature in all bacterial 16S rRNAs. We use all-atom molecular dynamics simulations to demonstrate that the co-evolving signature in the N-terminus of S4 is intrinsically disordered and capable of accelerating the 5WJ:S4 binding process through a fly-casting mechanism. The scenario is further confirmed using the structure-based Go model for protein:RNA, with which hundreds of simultaneous folding and binding events between the 5WJ and S4 are captured. Based on analysis of both explicit solvent MD and structure-based Go trajectories, we identify multiple metastable states of the 5WJ, and various protein-guided folding pathways that compare directly with the FRET experiments.

Computational Methods II

4057-Pos Board B785
Ligand Binding Pathways and Transitions in a Glutamate Receptor
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Ionotropic glutamate receptors (iGluRs) are ligand-gated ion channels that are responsible for the majority of excitatory transmission at the synaptic cleft. Mechanically speaking, agonist binding to the ligand binding domain (LBD) triggers a conformational change which is transmitted to the transmembrane region, opening the ion channel and activating the receptor. We present a computational study for examining the ligand-binding events and subsequent LBD closure in molecular detail for the iGluR subtype GluA2 . We develop and utilize several computational methodologies for analyzing and computing the free energies associated with different binding trajectories.

4058-Pos Board B786
A Thermodynamic Discrimination of Efficacy of GPCR Ligands using Absolute Binding Free Energy Calculations
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G-protein-coupled receptors (GPCRs) play fundamental roles in most physiological processes by modulating diverse signaling pathways and thus have become one of the most important drug targets. Based on the fact that a variety of the extracellular signals are mediated in a ligand-specific manner such as inverse agonist, neutral antagonist and agonist, quantitative characterization of the ligand efficacy is essential for rational design of selective modulators for GPCR targets. As experimental methods used for this purpose are time-, cost- and labor-intensive, computational tools, if they were systematically able to predict the efficacy of GPCR ligands, would make a big impact on GPCR drug design. To tackle this issue, in this study we apply free energy perturbation molecular dynamics (FEP/MD) simulations to calculating absolute ligand binding free energy for β_2-adrenergic receptor (β_2AR)/ligand systems. Based on the characterization of binding free energy change with respect to simulation time and free energy decomposition, we present that computationally measured thermodynamic properties can be used as promising descriptors for discriminating the efficacy of GPCR ligands. In addition, the simulation results also provide further insights into β_2AR activation dynamics and ligand binding affinity.